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10/525,292	10/27/2005	Hans-Juergen Krause	BBI-185US	6073

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,292	KRAUSE ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *1-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-12* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/1/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group III, claims 17-23, drawn to a pharmaceutical composition comprising an antibody, mannitol, Tween-80, and a buffer system in the reply filed on 17 December 2008 is acknowledged. The traversal is on the ground(s) that the claims are drawn to a single inventive concept and a single inventive effort, the search and examination of which would not place a serious burden on the Examiner. Applicant indicates that the claims are different aspects and embodiments of the same disclosed subject matter. Applicant argues that the present invention contains a single searchable unifying aspect, i.e., aqueous pharmaceutical antibody formulations. Applicant's arguments are found to be persuasive *in part*. The Examiner acknowledges that the claims in Groups II and III are drawn to a single inventive concept. Thus, the restriction requirement between Groups II and III is hereby *withdrawn*. Claims 13-15 of Group II are hereby *rejoined* to claims 16-23 of Group III. However, as discussed in the previous Election/Restriction requirement of 17 November 2008, the invention described in claim 1 is anticipated by Corbo et al. (U.S. 6,024,938). Since the first claimed invention fails to distinguish over the prior art, it does not have a special technical feature. It follows that it cannot share a special technical feature with the other claimed inventions. Additionally, inventions I and rejoined II/III as claimed require different ingredients, process steps, and endpoints, requiring a unique search of the prior art. For instance, Invention I simply requires search and consideration of a composition/formulation comprising an antibody in a buffered solution. Invention II/III requires search and consideration of a composition/formulation comprising an antibody, a polyol, a surfactant, and a buffer system comprising citrate and/or phosphate, which

is not required by the other invention. The distinct inventions require separate, distinct, and non-coextensive searches. As such, it would be burdensome to search the inventions of Groups I and rejoined II/III together.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 17 December 2008.

Claims 13-23 are under consideration in the instant application.

Claim Objections

1. Claims 16 and 21-23 are objected to because of the following informalities:

1a. Regarding claims 16 and 21-23, the acronym "TNFα" renders the claims vague and indefinite. Abbreviations should be spelled out in all independent claims for clarity.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 13-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claims 13-23 are indefinite because the elements recited in the claim do not constitute proper Markush groups. The claims are indefinite in the alternative use of "and/or" because it is not clear what controls which of these limitations. See claims 13, 17, 19 and MPEP § 2173.05(h).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 13-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Okada et al. (EP 1174148; 4/27/2000).

Okada et al. teach a pharmaceutical composition comprising a non-ionic surface agent (such as polysorbate 80; also known as Tween-80), (page 3, [0010]), a disaccharide (such as mannitol), and a buffer (such as a phosphate buffer or a citrate buffer) (page 3, [0010], [0012], [0014]), Okada et al. state the pH of the pharmaceutical composition is adjusted from 4 to 6 by the buffer (page 3, [0014]).

5. Claims 13-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Gombotz et al. (US 20030180287).

Gombotz et al. teach an aqueous pharmaceutical composition comprising an antibody or an Fc domain containing polypeptide, a buffer, tonicity modifier, and one or more excipients (page 1, [0006]; page 3, [0035-0036]; pages 4-5, [0052]). Gombotz et al. teaches that the composition may contain an antibody that recognizes tumor necrosis factor (TNF) (page 3, [0036]). Gombotz et al. disclose that the buffer maintains the composition pH at a range of about 6.0 and about 7.0 (page 1, [0006]; page 4, [0046]). Gombotz et al. teach that buffering agents include potassium phosphate and sodium or potassium citrate and that the concentration of the buffer is between about 1mM to about 1M (page 4, [0045]). Gombotz et al. disclose that a tonicity modifier includes mannitol (page 4, top of column 2, [0047]). Gombotz et al. teach that the concentration of the tonicity modifier is between about 1 mM to 1M (page 4, top of column 2, [0045]). Additionally, Gombotz et al. indicate that a suitable excipient to stabilize the polypeptide while in solution includes Tween-80 (also known in the art as polysorbate 80) (page 4, [0048]). Gombotz et al. indicate the concentration of the excipient is between about 0.001 to 5 percent weight percent (page 4, [0049]). Gombotz et al. teach that the formulation can comprise about 10 to about 100 mg/ml of the polypeptide (page 4, [0051]; page 8, claim 1).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 15, 17, 18, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okada et al. (EP 1174148; 4/27/2000) and Gombotz et al. (US 20030180287) as applied to claims 13 and 14 above.

The teachings of Okada et al. and Gombotz et al. are set forth above.

Okada et al. and Gombotz et al. do not recite the specific amounts (mg/ml) of antibody, mannitol, and Tween-80 recited in claims 15 and 17-19.

However, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the amounts of buffer, disaccharide/tonicity modifier (i.e., mannitol), and surface agent/excipient (i.e., Tween-80) utilized in the compositions as taught by Okada et al. and Gombotz et al. The person of ordinary skill in the art would have been motivated to make that modification to in order to improve upon what is already known, thus determining the optimum combination amounts of reagents. The person of ordinary skill in the art reasonably would have expected success because optimization of conditions is routine in the art. See *In re Aller* 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) "[W]here the general

conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation". See also *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). Therefore, the claimed invention as a whole is clearly *prima facie* obvious over the prior art.

7. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gombotz et al. (US 20030180287) as applied to claims 13-14 above, and further in view of Salfeld et al. (U.S. Patent 6,090,382).

The teachings of Gombotz et al. are set forth above.

Gombotz et al. does not disclose an aqueous pharmaceutical composition comprising an antibody that binds TNFα, particularly the antibody D2E7.

Salfeld et al. teaches TNFα is implicated in the pathophysiology of a variety of human diseases, such as shock, sepsis, infections, autoimmune diseases, transplant rejection and graft-versus-host disease (column 1, lines 10-20). Salfeld discloses that therapeutic strategies have been designed to inhibit or counteract hTNFα activity, in particular antibodies that bind to and neutralize hTNFα (column 1, lines 23-27). Salfeld et al. teach a recombinant anti-hTNFα antibody, termed D2E7, neutralizes hTNFα activity (column 2, lines 50-67; column 9, lines 43-67 through column 5). Salfeld et al. disclose administering an anti-hTNFα to a human subject

suffering from a disorder in which TNFα activity is detrimental such that human TNFα activity in the human subject is inhibited (column 4, lines 32-48; columns 24-27).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the aqueous pharmaceutical composition as taught by Gombotz et al. by substituting the antibody or an Fc domain containing polypeptide with the anti-hTNFα antibody, D2E7, as taught by Salfeld et al. The person of ordinary skill in the art would have been motivated to make that modification to provide a stable liquid formulation that allows long term storage of the antibody (see for example, Gombotz et al., page 1, [0005], [0023]). The person of ordinary skill in the art reasonably would have expected success because similar preparations were already being generated at the time the invention was made. Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

8. Claims 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gombotz et al. (US 20030180287) as applied to claims 15, 17, 18, and 19 above, and further in view of Salfeld et al. (U.S. Patent 6,090,382).

The teachings of Gombotz et al. are set forth above.

Gombotz et al. does not disclose an aqueous pharmaceutical composition comprising an antibody that binds TNFα, particularly the antibody D2E7.

Salfeld et al. teaches TNFα is implicated in the pathophysiology of a variety of human diseases, such as shock, sepsis, infections, autoimmune diseases, transplant rejection and graft-versus-host disease (column 1, lines 10-20). Salfeld discloses that therapeutic strategies have been designed to inhibit or counteract hTNFα activity, in particular antibodies that bind to and

neutralize hTNFα (column 1, lines 23-27). Salfeld et al. teach a recombinant anti-hTNFα antibody, termed D2E7, neutralizes hTNFα activity (column 2, lines 50-67; column 9, lines 43-67 through column 5). Salfeld et al. disclose administering an anti-hTNFα to a human subject suffering from a disorder in which TNFα activity is detrimental such that human TNFα activity in the human subject is inhibited (column 4, lines 32-48; columns 24-27).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the aqueous pharmaceutical composition as taught by Gombotz et al. by substituting the antibody or an Fc domain containing polypeptide with the anti-hTNFα antibody, D2E7, as taught by Salfeld et al. The person of ordinary skill in the art would have been motivated to make that modification to provide a stable liquid formulation that allows long term storage of the antibody (see for example, Gombotz et al., page 1, [0005], [0023]). The person of ordinary skill in the art reasonably would have expected success because similar preparations were already being generated at the time the invention was made. Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
27 February 2009

/Bridget E Bunner/
Primary Examiner, Art Unit 1647